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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/965,651	09/25/2001	Sanjay Kumar Nigam	15670/020001	3073

7590 07/26/2005

Joseph R. Baker, Jr.
Burns, Doane, Swecker & Mathis, LLP
402 West Broadway Suite 400
San Diego, CA 92101

EXAMINER	
WITZ, JEAN C	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,651	NIGAM, SANJAY KUMAR	
	Examiner	Art Unit	
	Jean C. Witz	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *9-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of species of tunicamycin and geldanomycin in the reply filed on April 29, 2005 is acknowledged. Applicant identified claims 1-5 and 7-8 as generic. Claim 6 recites one of the elected species. However, Applicant did not address new claims 9-14. Claims 9-13 recites classes of agents and specific agents that fall within those classes. Neither of the elected species are recited in the classes of agents recited in claims 9-13 while claim 14 recites both elected species and the class of agents to which they belong. Therefore, claims 9-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-8 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bush et al., American Journal of Physiology – Renal Physiology, 277: 211-218 (1999) combined with U.S. Patent 6,015,659 to Welch et al.

Claims 1-5 and 7-8 are generic to a method for enhancing recovery by epithelial cells from ischemia by targeting distinct lesions comprising contacting a lesion with a plurality of agents that act by a list of actions. Applicant elected the plurality of agents

to include tunicamycin and geldanomycin, which are explicitly recited in claims 6 and 14.

Bush et al. teaches that heat shock proteins (Hsps) and particularly those of the Hsp70 family, function to protect cellular proteins and protein biosynthetic processes following a variety of cell stresses including high temperature, hypoxia, alcohol, heavy metals and anoxia. Bush et al. also teaches that whole kidney ischemia and reperfusion as well as ATP depletion of cultured renal and thyroid epithelial cells increased not only the expression of cytosolic Hsps but also the expression of endoplasmic reticulum (ER) molecular chaperones which indicated that these ER chaperones also play an important role (along side the Hsps) in significantly increasing cell viability following ischemia. Pretreatment of kidney epithelial cell cultures with tunicamycin, an inducer of ER molecular chaperones that do not affect Hsp70 cytosolic expression, prior to ATP depletion resulted in increased expression of the ER molecular chaperones and cytoprotection as evidenced by significant (~80%) decreases in the level of cell injury in the tunicamycin-pretreated cells. Therefore, the authors conclude that pretreating cells with agents that induce ER molecular chaperones results in cytoprotection in the face of ATP depletion. Bush et al. does not discuss the effects of geldanomycin on the cells.

Welch et al. discuss the expression of heat shock proteins (Hsps) in cells in response to stresses such as heat and other treatments that elicit a stress response. Ischemia and reperfusion injury is identified at col. 4 as one of the treatments known to induce such a stress response as a result in the depletion of ATP levels in the

ischemic cells and results in the accumulation of abnormally folded proteins. The Hsp proteins so produced enable the stressed cells to more effectively withstand a subsequent and more severe stress that would otherwise do irreversible damage to the cells. One of the heat shock protein specifically discussed is Hsp72 (see col. 2). It is also well known that tolerance induced by one type of stressor, e.g. heat, is effective against subsequent exposure to other types of stressors, e.g. chemical agents).

Welch et al. teach that benzoquinonoid ansamycins and specifically geldanamycin (a synonym for geldanomycin) may be administered to cells that may be expected to experience a stress in order to stimulate production of Hsp proteins and therefore induce tolerance in the cells of the organism. The cells that may be so treated include epithelial cells and organs that may be so treated include kidneys (see col. 6). In Experiment 10 (col. 15), the kidneys of mice pretreated with geldanamycin showed dramatically increased levels of Hsp 72. Welch et al. does not discuss the effects of tunicamycin on the cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer both tunicamycin and geldanamycin to epithelial cells in order to improve the cells' response to ischemia with the expectation that the cells so treated will benefit from the additive effects of the two different pathways of protection. The motivation to do so is found implicitly in the statement of Welch et al. that geldanamycin provides benefits from heat shock protein stimulation combined with the statement of Bush et al. that tunicamycin stimulates production of endoplasmic reticulum chaperones whose effects are independent of the effects of the heat shock

proteins because one of ordinary skill in the art would wish to maximize the beneficial effect by combining the compositions, each taught individually to have a beneficial effect. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

It is noted that the actions recited in items (i) – (iv) are not explicitly addressed in the Welch et al. patents; however, Bush et al. identifies heat shock proteins as those that bind to misfolded or abnormal proteins and prevent their aggregation either by rescuing such proteins from irreversible damage or by increasing their susceptibility to proteolytic attack, and therefore, the disclosure of geldanamycin is deemed to inherently meet at least one of the cited actions.

Further, insofar as the prior art does not explicitly identify the presence and therefore the treatment of lesions, the prior art renders the treatment of lesions obvious to one of ordinary skill in the art. First, it is noted that there is no limitation in the claims to the number and degree of lesions in the epithelial cells. Second, it is clear from the disclosure that the lesions that are claimed comprise the protein abnormalities identified in Bush et al. Third, it is equally clear that the entire concept of protection as discussed in the prior art references is based upon a “pre-conditioning” of the cells via a preliminary stress event that causes the cells to be subjected to a stress condition that is, in the least, sub-lethal. In a natural setting, cells that have been stressed are

more resistant to further stress – a sort of a "strengthening" of the cellular mechanisms. As indicated by Welch et al., ischemia and ATP depletion is a stress equivalent to the chemical treatment or heat treatment discussed as a preliminary event. Absent objective evidence to the contrary, the prior art indicates that any sublethal stress can precondition and confer protection against any other type of stress (see patent to Welch et al., col. 2 where heat shock proteins are stimulated by chemical agents as well as heat stress and see col. 1 which teaches "cross-protection"). Further, Bush et al. suggestions that induction of ER chaperones could be useful in clinical settings, either as preemptive measures or to enhance recovery after injury. Since Bush et al. provides the separate but equivalent action of the ER chaperones to the heat shock proteins in protection, treatment is deemed to be motivated in response to any non-lethal stress (which inherently produces lesions) in order to stimulate continuous and expected protective cellular mechanisms in the same homeostatic manner as occurs naturally.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (571) 272-0927. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jean C. Witz
Primary Examiner
Art Unit 1651